REMARKS

Claims 1, 3-6 and 8-10 were examined. No claims are amended or added. Claims 1, 3-6 and 8-10 remain in the Application.

I. Claim Rejections – 35 U.S.C. §102(b)

The Patent Office rejects claims 1, 4, 6, 8 and 9 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,767,153 of Bowman et al. (Bowman).

The Patent Office states in the Office Action, on page 3, first paragraph, "Bowman et al. disclose in Table 1, a prostaglandin $F_{2\alpha}$ derivative, $PGF_{2\alpha}$-1-Isopropyl Ester, which is a synonym for Bimatoprost as disclosed by the disclosed Material Safety Sheet. Therefore, Bowman et al. encompass the limitation of the claims."

The Material Safety Data Sheet identifies Bimatoprost as 15(R)-17-phenyl trinor $PGF_{2\alpha}$ isopropyl ester. The omega chain of this molecule is a five carbon chain (carbon 13-carbon 17) and there is a phenyl group at carbon 17. "$PGF_{2\alpha}$-1-Isopropyl Ester" listed in Table 1 of Bowman is not Bimatoprost. "$PGF_{2\alpha}$-1-Isopropyl Ester" is "Dinoprost" as identified in **Reference 1** herein of Cayman Chemical. The omega chain of $PGF_{2\alpha}$-1-Isopropyl Ester includes an eight carbon chain and there is no phenyl group.

Applicant respectfully requests that the rejection of claims 1, 4, 6, 8 and 9 under 35 U.S.C. §102(b) be withdrawn.

II. Claim Rejections – 35 U.S.C. §103

The Patent Office rejects claims 2, 3 and 5 under 35 U.S.C. §103(a) as being obvious over Bowman as applied to claims 1, 4, 6, 8 and 9 above, and further in view of U.S. Patent No. 6,342,524 of Hellberg et al. (Herberg).

Claims 2 and 5 depend from claim 1 and therefore contain all the limitations of that claim. For at least the reason stated above with respect to claim 1, claims 2 and 5 are not obvious over the cited references.

(1) Bowman Reference

The Patent Office states in the office action, "Bowman discloses when poorly water soluble medicaments are dissolved in oil, their bioavailability to the targeted tissue may be enhanced, thus overcoming the solubility issues in an aqueous solution.

"Bioavailability" is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action and is related to absorption of the drug to the cite of action. See Goodman & Gilman's, the Pharmacological Basis of Therapeutics, attached hereto as **Reference 2**.

In the ophthalmic drugs, bioavailability generally relates to absorption of the drug through the cornea. The proportion or percentage of the drug to reach to the site of action has nothing to do with the stability of the drug in the preparation or formulation. The suppression of degradation of the drugs in the preparation is thus unrelated to the bioavailability of the drug.

Claims 2-3 and 5 relate to a pharmaceutical composition that, in one aspect, has an effect to prevent the degradation of the drug (prostaglandin, PG) and does not have any effect to raise or increase the solubility of the drug in the preparation.

(2) Hellberg Reference

Hellberg discloses therapeutic methods for treating glaucoma by the combined use of the drugs such as NSAID and PG. Hellberg does not mention any addition of oil such as MCT in the preparation, nor does it disclose concrete components of an emulsion.

Therefore, a person of skill in the art could not conceive the claimed oil-in-water emulsion comprising $PGF_{2\alpha}$ oil and water soluble polymer, which is capable of suppressing the degradation of the drug in the ophthalmic preparation.

(3) Schnedier Reference

U.S. Patent No. 5,631,287 of Schneider et al. (Schneider) discloses the use of polyoxyethylated castor oil to enhance the stability of PG in the preparation.

It is generally recognized that a PG is subject to hydrolyzation, and therefore, it is difficult to keep the drug stable in an aqueous composition.

The Patent Office states in the Office Action that prostaglandins are known to be hydrolytically unstable as taught by Schneider and, therefore, one would have expected the stability of the prostaglandin to increase in the oil-water vehicle of <u>Bowman</u> in view of <u>Hellberg</u>.

<u>Schneider</u> discloses, when polysorbate 80 is employed as a surfactant, a concentration of PG decreases to 10% of the initial concentration after 30 days of storage at 55°C. However, when polyoxyethylated castor oil is added to the composition, the concentration of PG is at 50% or of the initial concentration after 30 days of storage at 55°C (see Fig. 3).

The compositions disclosed in the Application, for example, formulations of 5 and 6, by contrast maintain almost 100% of the initial PG concentration relative to the initial concentration even after 4 weeks of 60°C, which is a more severe condition for storage than the above cases of <u>Schneider</u>. Such a special effect of the described and claimed composition could not be expected by one of skill in the art prior to Applicant's invention.

As mentioned above, there is no relation between the improvement of bioavailability described in <u>Bowman</u> and stabilization of the drug in the preparation, and <u>Hellberg</u> fails to state the addition of oils in the preparation. Therefore, the artisan would not conceive the stable PG composition from the combination of <u>Bowman</u> and <u>Hellberg</u>.

In addition, the claimed compositions demonstrate a much higher stability of the specific PG drugs than the compositions described in <u>Schneider</u>. For these reasons, claims 3 and 5 are not obvious under 35 U.S.C. §103(a) in view of the cited references.

(4) <u>Unexpected Result of PG Compounds Other Than "Latanoprost"</u>

The present emulsion of latanoprost, a typical example of PG compound, shows excellent stability of the drug in the aqueous composition as shown in Table 2 in the Application. A person of skill in the art can expect that other prostaglandin esters recited in pending claim 1 of the Application than latanoprost can be stabilized by emulsifying the formulation according to the composition of latanoprost.

CONCLUSION

In view of the foregoing, it is believed that all claims now pending patentably define the subject invention over the prior art of record and are in condition for allowance and such action is earnestly solicited at the earliest possible date.

If necessary, the Commissioner is hereby authorized in this, concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17, particularly extension of time fees.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR, & ZAFMAN LLP

Dated: 1/31/11

By: William Babbitt
William Thomas Babbitt, Reg. No. 39,591

1279 Oakmead Parkway
Sunnyvale, California 94085-4040
Telephone (310) 207-3800
Facsimile (408) 720-8383

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Nedy Calderon 1/31/11
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Reference /

Dinoprost.

Koufman

Cayman CHEMICAL

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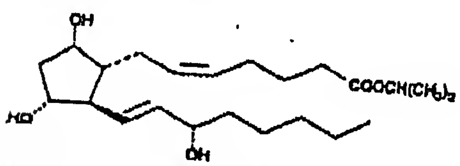
Like YouTube, Gmail, and Google Apps, we no longer support all site functions in Internet Explorer 6 and earlier.

Holiday Notification: Cayman Chemical will be closed December 24, 2010, through January 2, 2011, for the holidays. More...

Prostaglandin $F_{2\alpha}$ isopropyl ester

Cayman Chemical Item Number 16030

$PGF_{2\alpha}$ isopropyl ester; Dinoprost isopropyl ester (CAS 53764-90-2)



See more Prostaglandins (480)

Synonyms	PGF2α isopropyl ester Dinoprost isopropyl ester
Formal Name	9α, 11α, 15S-trihydroxy-prosta-5Z, 13E-dien-1-oic acid, isopropyl ester
CAS Number	53764-90-2
Molecular Formula	$C_{23}H_{40}O_5$
Formula Weight	396.6
Formulation	A solution in methyl acetate
Purity	>98%
Stability	2 years
Storage	-20°C
Shipping	WET ICE in continental US; may vary elsewhere
SMILES	CCCCC[C@H](O)/C=C/[C@H]1[C@H](O)C[C@H](O)[C@@H]1C/C=C\CCCC(=O)OC(C)C

Description

$PGF_{2\alpha}$ isopropyl ester is an ester prodrug of $PGF_{2\alpha}$ with enhanced lipid solubility. Due to better membrane penetration, $PGF_{2\alpha}$ isopropyl ester is more suitable than $PGF_{2\alpha}$ or $PGF_{2\alpha}$ tromethamine salt for topical application in studies on intraocular pressure. The ester functionality is readily hydrolyzed *in vivo* to release the active compound $PGF_{2\alpha}$. When administered topically to the eyes of cynomolgus monkeys, a 5 µg dose reduces intraocular pressure by 68% after the fourth day of treatment.[1]

Background Reading

Crawford, K.S., Kaufman, P.L. Dose-related effects of prostaglandin $F_{2\alpha}$ isopropyl ester on intraocular pressure, refraction, and pupil diameter in monkeys. *Invest Ophthamol Vis Sci* 32 510-519 (1991).

Prostaglandin F2α isopropyl ester is available in the following screening libraries:
Prostaglandin Screening Library I (96-Well)
Bio-active Lipid I Screening Library (96-Well)

Size	Price	Quantity	Subtotal
1 mg	$51.00		$0.00
5 mg	$230.00		$0.00
10 mg	$408.00		$0.00
50 mg	$1,785.00		$0.00
Bulk	Contact		
		Cart Total	$0.00

Pricing updated 2010-12-14. Prices are subject to change without notice.

Pricing is for North America only. Other customers should contact a distributor in their region.

Cayman strives to be a reliable biochemical reagent vendor by providing the best possible products and services. To ask for assistance with one of our products please contact a Technical Support Scientist.

Warning This product is not for human or veterinary use.

Related Products

17-phenoxy trinor Prostaglandin $F_{2\alpha}$ ethyl amide NEW exclusive
Latanoprost-d4
Prostaglandin $F_{2\alpha}$

Downloads

- Download Product Insert 149 Kb PDF
- Download Material Safety Data Sheet (MSDS) 18 Kb PDF
- Chemical structure definitions are available for many Cayman products. See Chemical Structure Database for details.

Reference 2

McGraw-Hill

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Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10/e

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these sites and also in the capillary endothelium of brain capillaries is P-glycoprotein, which is encoded by the multidrug resistance-1 (*MDR1*) gene. Important in resistance to cancer chemotherapeutic agents (Chapter 52). P-glycoprotein localized in the enterocyte also limits the oral absorption of transported drugs since it exports the compound back into the intestinal tract subsequent to its absorption by passive diffusion.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is concerned primarily with a parameter designated as *bioavailability*, rather than absorption. *Bioavailability* is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action. For example, a drug given orally must be absorbed first from the stomach and intestine, but this may be limited by the characteristics of the dosage form and/or the drug's physicochemical properties. In addition, drug then passes through the liver, where metabolism and/or biliary excretion may occur before it reaches the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is large, bioavailability will be substantially reduced (the so-called *first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (*see* below), and the choice of the route of drug administration must be based on an understanding of these conditions.

Oral (Enteral) *versus* Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 1–1.

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Disadvantages to the oral route include limited absorption of some drugs because of their physical characteristics (*e.g.*, water solubility), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the intestinal flora, mucosa, or the liver before they gain access to the general circulation.

The parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be delivered in its active form. Availability is usually more rapid, extensive, and predictable than when a drug is given by mouth. The effective dose therefore can be more accurately delivered. In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs, however, has its disadvantages: asepsis must be maintained; pain may accompany the injection; it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary; and there is the risk of inadvertent administration of a drug when it is not intended. Expense is another consideration.

Oral Ingestion. Absorption from the gastrointestinal tract is governed by factors such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug (solution, suspension, or solid dosage form), its water solubility, and concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may be the limiting factor in their absorption, especially if they have low water solubility. Since most drug absorption from the gastrointestinal tract occurs *via* passive processes, absorption is favored when the drug is in the nonionized and more lipophilic form. Based on the pH-partition concept presented in Figure 1–2, it would be predicted that drugs that are weak acids would be better absorbed from the stomach (pH 1 to 2) than from the upper intestine (pH 3 to 6), and *vice versa* for weak bases. However, the epithelium of the stomach is lined with a thick mucous layer, and its surface area is small; by contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely nonionized in the stomach. Thus, any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption, while any factor that delays gastric emptying will probably have the opposite effect, regardless of the characteristics of the drug.

Drugs that are destroyed by gastric juice or that cause gastric irritation sometimes are administered in dosage forms with a coating that prevents dissolution in the acidic gastric contents. However, some enteric-coated

for experts. The first-pass and cleansing effects of the lung are not available when drugs are given by this route.

Intrathecal. The blood-brain barrier and the blood–cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space. Brain tumors also may be treated by direct intraventricular drug administration.

Pulmonary Absorption. Provided that they do not cause irritation, gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route, because the lung's surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapters 13, 14, and 16.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and, in the case of pulmonary disease, local application of the drug at the desired site of action. For example, drugs can be given in this manner for the treatment of bronchial asthma (*see* Chapter 28). Past disadvantages, such as poor ability to regulate the dose and cumbersomeness of the methods of administration, have to a large extent been overcome by technological advances, including metered-dose inhalers and more reliable aerolizers.

Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states. Both local and systemic reactions to allergens may occur subsequent to inhalation.

Topical Application. *Mucous Membranes.* Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of synthetic antidiuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Skin. Few drugs readily penetrate the intact skin. Absorption of those that do is dependent on the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier (*see* Chapter 65). The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (*e.g.*, a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are becoming increasingly available. A patch containing scopolamine, placed behind the ear where body temperature and blood flow enhance absorption, releases sufficient drug to the systemic circulation to protect the wearer from motion sickness. Transdermal estrogen replacement therapy yields low maintenance levels of estradiol while minimizing the high estrone metabolite levels observed following oral administration.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (*see* Chapter 66). Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic receptor antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma thus may result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drugs are not administered as such; instead, they are formulated into drug dosage forms. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations has been a matter of concern. Strengthened regulatory requirements have resulted in few, if any, documented cases of nonequivalence between approved drug products. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

DISTRIBUTION OF DRUGS

Following absorption or administration into the systemic blood, a drug distributes into interstitial and intracellular fluids. This process reflects a number of physiological factors and the particular physicochemical properties of the individual drug. Cardiac output, regional blood flow, and tissue volume determine the rate of delivery and potential amount of drug distributed into tissues. Initially, liver, kidney, brain, and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin,